CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-025

MEDICAL REVIEW(S)

Review of Clinical Data

Mortality in ENA-INT-03 "Lewy Body Demitia Trial"

NDA:	**20-823**
IND:	**35774**
Sponsor:	**Novartis**
Drug:	**Rivastigmine**
Route of Administration:	**Oral**
Reviewer:	**Greg Burkhart, M.D., M.S.**
Review Completion Date:	**August 13, 1999**

On May 12, 1999, the agency issued an AE letter for rivastigmine, a treatment for Alzheimer's Disease. However, in the letter we expressed continued concern about excess mortality in the RCTs and slightly greater mortality at higher doses in the open extensions to the RCTs. The letter requested that Novartis analyze data from several thousand patients that had not been included in previous analyses to see if greater mortality at the highest doses persisted. These additional analyzes were to use the same techniques as those in previous analyzes.

In an August 4 meeting to discuss Novartis's plan to address the issues raised in the AE letter, they presented data showing that there had been 2 deaths within 7 days of the last dose of placebo in protocol ENA-INT-03, a study of rivastigmine in Lewy body dementia that had recently completed. On August 9, Novartis submitted a summary of this study, its protocol, narratives for the placebo deaths, and some descriptive statistics of its participants.

In short, the study enrolled fairly similar patients as those in the RCTs included in the NDA although they tended to be slightly older (46% were >= 75 compared to 42% in the RCTs) and were more likely to male (53% compared to 42% in RCTs). The only deaths were in placebo with both events that lead to death beginning within 7 days of the last dose of placebo. Both deaths were due to pneumonia. The AE profile in the study was similar to that seen with rivastigmine in the NDA.

In my April 27, 1999 review of Novartis's response to the NA letter, I described the aggregate findings in the NDA as still representing a weak signal of concern. The signal was based upon excess mortality in the RCTs (3 deaths verse 0 within 7 days of the last dose) and greater mortality at 10/12 mg than lower doses in the open experience (using

FDA classified deaths the mortality was 13.2 at 10/12 mg compared to 9.3 at lower doses [per 1000 person-years]).

The 2 deaths that have now been observed with placebo in an RCT with a similar population to that in the RCTs included in the NDA have a significant impact on my interpretation of the experience collected to date with rivastigmine. I no longer consider the mortality experience to represent any signal of concern. The greater mortality at 10/12 mg compared to lower doses in the NDA is not surprising given the non-random nature of determining a patient's dose. Likewise, there is nothing about the deaths that suggest a cause for concern. (Both of these points are discussed in detail in my April 27 review.)

My only recommended action is ask DSI to inspect ENA-INT-03, since the interpretation of the mortality experience with rivastigmine could turn on the experience of 2 placebo patients from a small study. I do not believe there is any need for a randomized study to clarify the safety of rivastigmine. Likewise, in my opinion, the additional 3000-4000 patients need only a standard safety update prior to approval, and finally, there is no need to discuss the mortality experience in labeling.

The experience in ENA-INT-03 may also impact the hold issued for [redacted] since the safety concern about mortality was mentioned as a contributing factor in the decision to issue the hold.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

Brand Name:	**Exelon Oral Solution**
Generic Name:	**Rivastigmine**
Sponsor:	**Novartis**
Indication:	**Alzheimer's Disease**
NDA Number:	**21025**
Original Receipt Date:	**11/19/98**
Clinical Reviewer:	**Ranjit B. Mani, MD**
Review Author:	**Ranjit B. Mani, MD**
Review Completed:	**8/24/99**

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1. INTRODUCTION

The sponsor has resubmitted a New Drug Application for Exelon® Oral Solution. The sponsor's proposed indication for its use is the treatment of mild-to-moderately severe dementia of the Alzheimer's type.

Exelon® (rivastigmine, ENA 713) is a reversible cholinesterase inhibitor

The sponsor has already submitted NDA 20-823 for Exelon® Capsules; the proposed indication for their use is also the treatment of mild-to-moderately severe dementia of the Alzheimer's type. That application is currently under review. A "not-approvable" letter was issued by the Division on July 7, 1998, to which the sponsor has provided a Complete Response dated November 11, 1998 (see below).

The original submission of NDA 21-025 was made on August 11, 1998 and consisted of :

1. A single new bioequivalence study (# B153) comparing Exelon® Oral Solution with Exelon® Capsules (a full study report is provided)
2. Chemistry, Manufacturing and Controls data pertaining to the Exelon® Oral Solution form
3. Draft labeling

The remainder of that NDA was cross-referenced to NDA 20-823.

In a letter dated October 2, 1998, this Division refused to file NDA 21-025 on the grounds that the application was not sufficiently complete to merit review: it failed to provide full reports of all tests necessary to show that rivastigmine was safe for use under the conditions proposed for its use in the treatment of Alzheimer's disease. The Division's conclusion was based on the following 2 considerations:

1. That the application was not in and of itself a complete NDA, but relied on information contained in reports made (or which were to be made) to the unapproved NDA 20-823 for the capsule formulation of rivastigmine
2. That, at the time of the letter, NDA 20-823 was considered "not approvable"

Thus any NDA that relied for its approval on NDA 20-823 would also not be considered potentially approvable.

In the current submission the sponsor refers to its "Complete Response" submission under NDA 20-823 dated November 11, 1998; that submission was intended to repair all deficiencies in NDA 20-823 and discuss all issues raised in the Division' s "not approvable" letter dated July 7, 1998. The sponsor argues that NDA 21-025 should therefore be fileable. The "Complete Response" submission under NDA 20-823 was under review by this Division at the time this submission was received.

Exelon® Oral Solution has been studied in this country under IND application # [redacted] which resides in this Division.

The contents of the original submission under NDA 21-025 are replicated below, along with additional basic pre-clinical information about the drug derived from NDA 20-823.

2. EVENTS SINCE SUBMISSION

This submission was determined by the Division to be fileable at a meeting held on 1/15/99.

In regard to NDA 20823 for Exelon® capsules the following has occurred

- Based on the Complete Response to the non-approval letter, subsequent submissions, analyses performed both by the sponsor and by the Division, and face-to-face discussions, an approvable letter was issued by Dr R. Temple, Office Director, on 5/12/99. However, the letter indicated that prior to the application being approved, the sponsor should address a number of specific issues related to the following aspects of the application: mortality and other safety data, package insert, and professional sample package labeling/brochure. The most important of these issues was as follows: a continued suggestion, albeit weak, that Exelon® could have an unrecognized life-threatening risk
- The sponsor provided a response to the approvable letter on 6/8/99; please see my review of that response which was also a briefing document for a meeting with the Division on 8/4/99. At the meeting with the Division on 8/4/99, the sponsor presented a tabular summary of the mortality analysis for all randomized placebo-controlled trials completed to date. These included data from a recently completed European trial (# ENA-INT-03) of Exelon® in Lewy Body Dementia. The pooled mortality analysis for all randomized controlled trials, no longer showed a higher mortality rate for Exelon® than for placebo. Based on this information, and pending formal review of the data from the European trial referred to above, the sponsor was told that the Agency no longer had a concern about excess mortality in patients treated with Exelon® as compared with those treated with placebo and that a further mortality analysis was not needed. On 8/9/99 the sponsor submitted a summary of Study # ENA-INT-03, including the protocol, narratives for placebo deaths, and descriptive statistics for baseline demographic characteristics; this summary tended to reinforce the Division's conclusions.
- A safety update for Exelon® is awaited following which a further action regarding NDA 20823 is expected to be taken.

3. CHEMISTRY

Rivastigmine has the following chemical name: (S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenyl carbamate. The definitive form of the drug is the hydrogen tartrate salt, but doses used in humans are usually expressed in terms of the free base; the multiplication factor used to convert dose of hydrogen tartrate salt to that of free base is 0.625. The salt is very soluble in water and methanol, and is stable for up to 5 years, regardless of climatic conditions, if stored in very tight packaging.

Exelon® oral solution contains 2 mg/ml of rivastigmine base. Please see the NDA Chemistry Review for further details. Dr Janusz Rzeszotarski, Chemistry Reviewer, has recommended approval of this formulation

4. BASIC PHARMACOLOGY

Rivastigmine is a carbamate-type inhibitor of acetylcholinesterase. Like acetylcholine, carbamate-type inhibitors act as substrates for that enzyme, but form a carbamylated, rather than an acetylated complex with acetylcholinesterase. The carbamylated form is incapable of catalyzing the hydrolysis of acetylcholine thus prolonging its availability at the synaptic cleft; that function is restored only after the carbamylated enzyme is itself hydrolyzed and reactivated. However the hydrolysis and reactivation of carbamylated acetylcholinesterase is slow, with a half-life of > 24 hours for rivastigmine; this phenomenon is referred to as "pseudo-irreversible inhibition". In addition, the interaction of rivastigmine with acetylcholinesterase results in the formation of a metabolite, NAP 226-90, which itself has a minimal ability to inhibit the enzyme; this metabolic pathway is the major mode of clearance of rivastigmine. Acetylcholinesterase inhibition is believed to be the means of action of the drug in treating Alzheimer's disease. In rat brain such inhibition is more potent in the hippocampus and neocortex, than in other brain regions.

5. HUMAN PHARMACOKINETICS

The following information is based on studies <u>other</u> than those that used the Exelon® Oral Solution form of the drug

Studies have so far been performed in humans, involving normal subjects as well as those with cirrhosis, renal failure, depression, normal pressure hydrocephalus, depression and Alzheimer's disease. While most studies have involved the standard capsule form, for which a NDA is pending, other trials have involved slow-release oral, transdermal and intravenous formulations. The drug is well-absorbed when administered orally, but administration with food slows absorption (t_{max} delayed by 1.4 to 1.6 hours; C_{max} decreased and AUC increased by approximately 30 %, compared with fasting. However since nausea and vomiting may be related to the rate of rise of plasma concentrations and/or the magnitude of C_{max}, intake with food is recommended. The drug is weakly (approximately 40 %) bound to plasma proteins and after intravenous administration has a volume of distribution of 1.8 - 2.7 liters/kg, suggesting distribution to an extravascular compartment; it does appear to penetrate the blood-brain barrier. In addition to its metabolic clearance by interaction with acetylcholinesterase at the synapse as noted, the parent drug is hydrolyzed to NAP 226-90 by esterases, including acetylcholinesterase, in the liver and, to a lesser extent, intestine. NAP 226-90 may then undergo N-demethylation and/or conjugation. The parent drug has an elimination half-life of 0.8 - 1.25 hours across the age range in humans. It is only weakly bound to cytochrome P450 isoenzymes. Renal elimination of

radiolabelled oral ENA 713 is > 90 % complete after 24 hours; less than 1 % of the radioactivity in that form of the drug was detected in the feces. Neither ENA 713 nor NAP 266-90 accumulates with a twice daily oral regime of 2-12 mg/day and a steady state is reached by the second by the second dose. The half-life and AUC are higher, with oral dosing, in the elderly than in younger subjects. Plasma concentrations of ENA 713 and NAP 266-90, after oral dosing, are higher in patients with Alzheimer's disease than in normal subjects. In individuals with impaired renal function, the elimination of the metabolite appears to be reduced; however multiple oral 3 mg doses have been well-tolerated in patients with impaired liver or renal function. Pharmacokinetic interactions with drugs which are highly protein-bound or metabolized by cytochrome P450 isoenzymes are not expected based on in-vitro testing and on-vivo studies in humans using digoxin, warfarin, diazepam and fluoxetine with single doses of oral rivastigmine. No pharmacodynamic interactions have been seen with digoxin or warfarin. In all clinical trials of rivastigmine in patients with Alzheimer's disease, clinically relevant pharmacodynamic or pharmacokinetic interactions with a wide variety of concomitant medications were very infrequent.

6. STUDY B153

A full study report has been provided.

Title A Bioequivalence Study Comparing Single Doses of 3 mg and 6 mg of an Oral Solution of ENA 713 with 3 and 6 mg capsules in Patients with Probable Alzheimer's Disease

Objective To assess the bioequivalence of single 3 mg and 6 mg doses of a rivastigmine oral solution compared to 3 mg and 6 mg rivastigmine capsules, respectively, in patients with probable Alzheimer's disease.

Design Open-label, randomized (in regard to sequence of capsule and oral solution), crossover, inpatient study

Sample Size 53 patients, of whom 27 were assigned to the 3 mg cohort, and 26 to the 6 mg cohort.

6.1 Key Inclusion Criteria

- probable Alzheimer's disease, participating in open-label extensions of protocols B353, B355 and B357, receiving rivastigmine 6-12 mg/day
- < 86 years of age (if older must be approved by sponsor); if female, must not be of child-bearing potential
- written informed consent from patient (or legally authorized representative if patient is incompetent to provide consent) and from caregiver

6.2 Key Exclusion Criteria

- any medical condition that would place them at special risk for participating in the study
- loss or withdrawal of ≥ 1 pint (450 ml) of blood within one month before receiving study medication

- cardiac, renal, or hepatic disease or other conditions that could alter the pharmacokinetics of rivastigmine

6.3 Concomitant Medications

- dose of rivastigmine capsules used before trial will need to be altered or discontinued temporarily
- no other medication restrictions are listed by sponsor

6.4 Dosage

- dosage forms to be used in this trial were capsules of 3 mg and 6 mg , and an oral solution containing 2 mg/ml
- all patients entering this trial were to be on a 3 to 6 mg b.i.d. dosing regime from their previous study
- on Day minus 3 of this protocol, patients were to take their morning dose of rivastigmine from the previous study and would then suspend their normal dosing regime until they had completed participation in the current protocol
- patients who received doses ranging from 3 mg b.i.d. through 5 mg b.i.d. in the previous study were be assigned to receive the 3 mg dose during the current protocol; those who received 6 mg b.i.d. during the previous study were to be assigned to receive the 6 mg dose during the current protocol
- on Day 1 of the current study patients were to receive a single dose of rivastigmine in the morning; the dose strength was to be based on the criteria outlined above; whether the capsule or oral solution was to be administered would be based on randomization
- no further doses of rivastigmine were to be administered on Day 1; no rivastigmine was to be administered on Days 2 and 3
- on Day 4 a single dose of rivastigmine was to be administered in the morning, with no doses later that day; the dose strength was to be identical to what was used on Day 1; the oral formulation used was not to be that administered on Day 1
- on the evening of Day 5, patients were to be restarted or would begin titration to the dose of rivastigmine capsules that they were taking prior to the current study provided they were able to tolerate the latter medication

6.5 Outcome Measures

Pharmacokinetic parameters to be derived included AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, t_{max} and $t_{1/2}$

Safety parameters were to include vital signs and adverse events

6.6 Analysis Plan

- **safety** analysis was to be performed on all subjects entered into the study who have received at least one dose of study medication; **pharmacokinetic** analysis was to be performed on all subjects with plasma concentration versus time profiles for both the capsules and oral solution
- pooled descriptive statistics was to be provided for demographic and background variables

- abnormal vital signs would be displayed and identified by subject and treatment
- adverse events would also be displayed and identified by treatment
- pharmacokinetic parameters for rivastigmine and its metabolite would be summarized according to formulation and dose; log-transformed C_{max}, AUC_{0-24} and $AUC_{0-\infty}$ would also be summarized for rivastigmine
- pharmacokinetic parameter analysis and evaluation of bioequivalence would be performed separately for the 3 mg and 6 mg cohorts
- an ANOVA model would be used to evaluate the bioequivalence between capsule and solution in terms of the log-transformed pharmacokinetic parameters referred to above
- for each of those pharmacokinetic parameters bioequivalence between capsule and solution would be claimed if the corresponding confidence interval of ratio (solution/capsule) fell between 0.80 and 1.25.
- power calculation: based on the results of a previous bioequivalence study the sponsor had estimated that 22 subjects in each of the 3 mg and 6 mg cohorts would be needed to achieve an 80 % chance of claiming equivalence

6.7 Results

27 patients were assigned to the 3 mg cohort and 26 patients were assigned to the 6 mg cohort

Pharmacokinetic: Based on results for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of both rivastigmine and NAP 226-90, the 3 mg and 6 mg doses of the solution dosage form (2 mg/ml) were bioequivalent to the 3 mg and 6 mg capsule dosage forms. The following 2 tables summarize the data

Assessment of bioequivalence between solution and capsule for rivastigmine

Parameter	Geometric mean		% Difference	p-value	90% C.I.
	3 mg Solution (N=26)[b]	3 mg Capsule (N=26)[b]			
AUC_{0-t} (ng.h/mL)	17.65	17.90	-1.39	0.74	90-107%
$AUC_{0-\infty}$ (ng.h/mL)	19.01	18.84	0.90	0.85	94-109%
C_{max} (ng/mL)	7.60	8.0	-4.97	0.44	86-106%
t_{max}[a] (h)	1.0	1.0	0.0	0.09	—
Parameter	**Geometric Mean**		**% Difference**	**p-value**	**90% C.I.**
	6 mg Solution (N=26)	6 mg Capsule (N=26)			
AUC_{0-t} (ng.h/mL)	64.14	69.06	-7.13	0.06	87-99%
$AUC_{0-\infty}$ (ng.h/mL)	65.69	70.53	-6.85	0.08	87-100%
C_{max} (ng/mL)	22.24	22.65	-1.78	0.80	87-110%
t_{max}[b] (h)	0.75	1.0	-25.0	0.02*	—

C.I. = Confidence Interval
[a] For t_{max}, median values were provided instead of geometric mean and the significance level was obtained from the Wilcoxon signed rank test.
[b] Excluding Patient 1016 who did not have complete pharmacokinetic profile for both periods of the study
* = statistically significant, p≤0.05

Assessment of bioequivalence between solution and capsule for NAP 226-90

Parameter	Geometric mean		% Difference	p-value	90% C.I.
	3 mg Solution (N=26)[b]	3 mg Capsule (N=26)[b]			
AUC_{0-t} (ng.h/mL)	30.69	31.60	-2.86	0.31	92-102%
$AUC_{0-\infty}$ (ng.h/mL)	34.06	33.85	0.60	0.95	95-106%
C_{max} (ng/mL)	5.95	6.0	-0.80	0.77	93-105%
t_{max}[a] (h)	1.5	1.5	0.0	0.28	
Parameter	**Geometric mean**		**% Difference**	**p-value**	**90% C.I.**
	6 mg Solution (N=26)	6 mg Capsule (N=26)			
AUC_{0-t} (ng.h/mL)	61.81	63.94	-3.34	0.08	93-100%
$AUC_{0-\infty}$ (ng.h/mL)	64.97	68.10	-4.59	0.03*	92-99%
C_{max} (ng/mL)	10.51	9.97	5.34	0.27	97-114%
t_{max}[a] (h)	1.25	1.5	-16.67	0.08	

C.I. = Confidence Interval
[a] For t_{max}, median values were provided instead of geometric mean and the significance level was obtained from Wilcoxon signed rank test.
[b] Excluding Patient 1016 who did not have complete pharmacokinetic profile for both periods of the study.
* =statistically significant, p≤0.05.

Safety:

- No deaths, serious or severe adverse events or adverse events leading to treatment discontinuation were noted
- The most frequently reported treatment-emergent adverse events (seen in > 7 % of subjects) were headache, diarrhea, nausea and insomnia, all of which were reportedly mild and transient.
- The following adverse events were seen in ≥ 5 % of patients in any of the 4 dose groups and more frequently overall when receiving the solution than when receiving the capsule: diarrhea and accidental trauma.
- The following table, copied from the submission, compares the incidence of treatment-emergent adverse events in each of the 4 dose groups

Treatment emergent adverse events by body system and formulation within dose

Body System/ *Preferred Term*	3 mg solution N=27 *n* (%)		3 mg capsule N=27 *n* (%)		6 mg solution N = 26 *n* (%)		6 mg capsule N = 26 *n* (%)	
At Least One Event	7	(26)	10	(37)	10	(38)	7	(27)
Any Drug Related Event	2	(7)	0	(0)	3	(12)	2	(8)
GASTRO-INTESTINAL SYSTEM DISORDERS	4	(15)	2	(7)	3	(12)	3	(12)
DIARRHEA	2	(7)	0	(0)	1	(4)	2	(8)
NAUSEA	1	(4)	1	(4)	1	(4)	1	(4)
CONSTIPATION	0	(0)	2	(7)	0	(0)	0	(0)
DYSPEPSIA	1	(4)	0	(0)	0	(0)	0	(0)
HICCUP	0	(0)	0	(0)	1	(4)	0	(0)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	2	(7)	5	(19)	2	(8)	1	(4)
HEADACHE	2	(7)	4	(15)	2	(8)	1	(4)
DIZZINESS	0	(0)	1	(4)	0	(0)	0	(0)
PSYCHIATRIC DISORDERS	3	(11)	3	(11)	1	(4)	0	(0)
INSOMNIA	1	(4)	3	(11)	0	(0)	0	(0)
AGITATION	1	(4)	1	(4)	1	(4)	0	(0)
ANXIETY	0	(0)	1	(4)	0	(0)	0	(0)
CONFUSION	1	(4)	0	(0)	0	(0)	0	(0)
DEPRESSION	1	(4)	0	(0)	0	(0)	0	(0)
BODY AS A WHOLE - GENERAL DISORDERS	1	(4)	1	(4)	3	(12)	1	(4)
ACCIDENTAL TRAUMA	0	(0)	0	(0)	2	(8)	1	(4)
FEVER	1	(4)	1	(4)	1	(4)	0	(0)
MUSCULO-SKELETAL SYSTEM DISORDERS	2	(7)	1	(4)	1	(4)	0	(0)
BACK PAIN	1	(4)	1	(4)	0	(0)	0	(0)
ARTHROSIS	0	(0)	0	(0)	1	(4)	0	(0)
PAIN	1	(4)	0	(0)	0	(0)	0	(0)
RESPIRATORY SYSTEM DISORDERS	1	(4)	1	(4)	1	(4)	1	(4)
RHINITIS	0	(0)	1	(4)	1	(4)	1	(4)
COUGHING	1	(4)	0	(0)	0	(0)	0	(0)
APPLICATION SITE DISORDERS	0	(0)	1	(4)	1	(4)	1	(4)
APPLICATION SITE REACTION*	0	(0)	1	(4)	1	(4)	1	(4)
HEARING AND VESTIBULAR DISORDERS	0	(0)	0	(0)	1	(4)	0	(0)
TINNITUS	0	(0)	0	(0)	1	(4)	0	(0)
RESISTANCE MECHANISM DISORDERS	0	(0)	0	(0)	1	(4)	0	(0)
UPPER RESP TRACT INFECTION	0	(0)	0	(0)	1	(4)	0	(0)

Only adverse events on the day of dosing and the day after dosing are tabulated.
Patients having the same type of AE after the sol and cap treatments were included in the tabulations for both treatments.
*Application site reactions include: erythema or bruising at the sites were the PK blood samples were drawn.

- Clinically notable pulse and blood pressure abnormalities are summarized in the following table. Most vital sign abnormalities were asymptomatic pulse and blood pressure fluctuations that resolved spontaneously; in a single

patient a persistently low diastolic blood pressure was attributed to concurrent treatment with diltiazem the dose of which was reduced.

Number of patients with clinically notable blood pressure and pulse abnormalities by treatment group

Variable		3 mg		6 mg	
		solution n (%)	capsule n (%)	solution n (%)	capsule n (%)
Total no. patients studied		27	27	26	26
Total no. patients with any clinically notable vital sign abnormality		6 (22)	7 (26)	9 (35)	6 (23)
Pulse	high	1 (4)	0 (0)	0 (0)	0 (0)
	low	0 (0)	1 (4)	1 (4)	2 (8)
Systolic BP	high	0 (0)	0 (0)	1 (4)	0 (0)
	low	2 (7)	1 (4)	3 (12)	1 (4)
Diastolic BP	high	0 (0)	0 (0)	0 (0)	0 (0)
	low	3 (11)	5 (19)	4 (15)	3 (12)

Patients having the same type of vital sign abnormality after sol and cap treatments were included in the tabulations for both treatments

6.8 Comments of Clinical Pharmacology and Biopharmaceutics Reviewer

The OPCB reviewer for this submission is Sayed Al-Habet, Ph.D. Please see his review for full details. His review was summarized at a meeting with our Division on 6/24/99.

Dr Al-Habet has concluded that:

- The 3 mg and 6 mg doses of the Exelon® oral solution are bioequivalent to the same doses, respectively of the Exelon® capsule
- As with the capsule formulation, the pharmacokinetics of the oral solution showed considerable variability across individuals
- The pharmacokinetics of Exelon® are non-linear

7. DRAFT LABELING

- The text of the draft package insert supplied in this submission contains all the information in the revised draft labeling for Exelon® capsules submitted on 8/27/97 in the 120-Day Safety Update for NDA 20-823. The draft label supplied with NDA 20-823 has already been reviewed by the Division, modified based on new information, attached to the approvable letter and possible modifications have already been discussed between the sponsor and Division
- The draft package insert enclosed in this submission is different from that submitted under NDA 20-823 only in the Description, Dosage And Administration and How Supplied sections
- The draft package insert enclosed in this submission is outdated
- —
  —
  —
- The sponsor has indicated that a combined package insert for the oral solution and capsule formulations of Exelon® may be pursued

- A formal review of the draft labeling supplied with this submission seems unnecessary at this time

8. COMMENTS AND CONCLUSIONS

- Exelon® oral solution and Exelon® capsules in 3 mg and 6 mg doses appear to be bioequivalent
- There appear to no Chemistry, Manufacturing and Controls deficiencies in this NDA that would preclude approval.
- Based on limited patient exposure, there do not appear to be major differences in the safety and tolerability of the Exelon® oral solution, in 3 and 6 mg doses in comparison the same doses, respectively of the Exelon® capsule
- NDA 20-823 for Exelon® capsules in the treatment of mild to moderate Alzheimer's Disease has been designated as being approvable. A further safety update is currently awaited prior to a further action on this NDA
- Based on the above, NDA 21-025 for Exelon® oral solution may be designated "approvable" as well
- Although the sponsor has proposed that the indication for Exelon® oral use be the treatment of "mild to moderately severe" dementia, the Division has already notified the sponsor that there is no difference in meaning between the phrases "mild to moderate" and "mild to moderately severe", at least in relation to claims for the treatment of Alzheimer's Disease.

9. RECOMMENDATIONS

I would recommend that NDA 21-025 for the use of Exelon® oral solution in the treatment of mild to moderate Alzheimer's Disease be designated "approvable". Further actions in regard to this NDA will in all likelihood needed to be linked to those for NDA 20-823 for Exelon® capsules.

/S/

Ranjit B. Mani, M.D.
Medical Reviewer

/S/

R. Levin, M.D.

rbm 8/24/99
cc:
HFD-120
NDA 21025
electronic copy-Levin
Nighswander

The sponsor has provided evidence that the 3 and 6 mg capsules are bioequivalent to 3 and 6 mg of the oral solution. However, without a complete review of the response to the approvable letter for NDA 20-823, there is insufficient information to determine if the drug is safe for the treatment of Alzheimer's disease and complete labeling for the drug. Therefore, this NDA cannot be approved until NDA 20-823 is approved. RL

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Center for Drug Evaluation and Research
Food and Drug Administration

Date: April 7, 2000
From: Randy Levin, M.D., Neurology Team Leader
Subject: NDA 21-025 Exelon Oral Solution
To: File

Background

NDA 21-025 was submitted on August 11, 1998 and included a bioequivalence study comparing the solution with the capsule, chemistry, manufacturing and control information, and draft labeling. The sponsor referred to NDA 20-823, the application for Exelon capsules, for evidence that the drug was safe and effective. Since the division had determined that NDA 20-823 was not approvable, the oral solution could not be approvable and the division refused to file the application on October 2, 1998. On November 11, 1998, the sponsor submitted a complete response to NDA 20-823, addressing the issues of the not approvable action and then resubmitted NDA 21-025.

On May 12, 1999, an approvable letter was issued for NDA 20-823 and the sponsor responded to the approvable letter on June 8, 1999. The due dates for NDA 20-823 and 21-025 are April 21, 2000 and April 22, 2000, respectively.

Chemistry, Manufacturing and Control

Drs. Rzeszotarski and Guzewska reviewed the cmc section of the submission and subsequent amendments addressing specific cmc issues and found the information adequate for approval. They recommended changes to the packaging to remove the word "new" from the carton label. In the labeling, the storage temperature should be 25 degrees centigrade.

Nonclinical toxicology

Drs. Rosloff and Fitzgerald reviewed the submission and that no toxicology studies beyond that submitted in NDA 20-823 were needed. There were no unusual excipents in the new formulation.

Clinical Pharmacology and Biopharmaceutics

Drs. Al-Habet and Baweja reviewed the biequivalence studies from NDA 20-823 and 21-025. They concluded that the 3 and 6 mg doses of the solution and capsules were bioequivalent. They noted that there was high variability between subjects and that the drug follows non linear kinetics with a greater proportional increase in both the Cmax and AUC with increasing doses from 3 to 6 mg. Since the clearance decreases with increasing doses, this suggests a saturation in the metabolic pathway. This may lead to increased toxicity with smaller dose changes. The bioavailability of the solution is 100% for the 3 mg dose and 90% for the 6 mg dose.

Clinical Safety

Dr. Mani reviewed the clinical safety portion of the package and did not find any new safety issues from the study.

Labeling

The sponsor has provided draft labeling based on the labeling provided with NDA 20-823. Changes in the labeling specific to the oral solution includes a description of the solution in the Description section, how to administer in the Dosage and Administration section, and additional information in the how supplied section.

Recommendations

The sponsor has provided sufficient information to show that the oral solution is bioequivalent to the capsules. The approval and labeling for this product is dependent on the action taken for NDA 20-823. At this time, the application is approvable. The labeling should be the same as with the capsule except for the information specific to the description and use of the solution.

/S/

Randy Levin, M.D.
Neuroiogy Team Leader

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